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Original article

N^1,N^1-Dimethyl-N^3-(3-(trifluoromethyl)phenethyl)propane-1,3-diamine, a new lead for the treatment of human African trypanosomiasis

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ABSTRACT

The natural product, convolutamine I (**1**), has anti-trypanosomal activity however it has a high molecular weight of 473 due to a presence of 3 bromine atoms. The synthesis of the natural product convolutamine I (**1**) together with its analogues are presented. A SAR study against *Trypanosoma brucei brucei* led to compounds with improved physico-chemical properties: lower molecular weight and lower log *P* while maintaining potency (with a slight 2-fold improvement).

1. Introduction

Human African trypanosomiasis, also known as African sleeping sickness, is endemic in the regions of sub-Saharan Africa, affecting around 70 million people in 36 countries [1]. The disease is caused by protozoa of the species *Trypanosoma brucei* and transmitted through the bite of an infected tsetse fly or passed from mother to child as the parasite can pass the placenta and infect the foetus. At the early stage, the trypanosomes multiply in subcutaneous tissues, blood and lymph and patients develop insignificant symptoms such as fever, headaches, joint pains and itching. In time, the parasites cross the blood–brain barrier and infect the central nervous system and patients start to develop confusion, sensory disturbances, poor coordination and sleep cycle disturbance. Without treatment, African sleeping sickness is fatal [1]. Current treatment for the neurological stage includes melarsoprol, an arsenical derivative known to have many undesirable or fatal (3–10%) side effects, resistance is developing and there is a failure rate of up to 30% [2]; eflornithine which is less toxic, has compliance issues and is only effective against the *Trypanosoma brucei gambiense* subspecies [3]; or a combination treatment of nifurtimox and eflornithine which is less toxic but not effective against the *Trypanosoma brucei rhodesiense* subspecies [1]. New, safe and effective drugs are urgently needed. As part of a continuing study for novel entities with high efficacy and less toxicity for human African trypanosomiasis, we have previously described the active natural product, convolutamine I (**1**), isolated from the bryozoan *Amathia tortusa* [4]. In order for a new drug to combat human African trypanosomiasis at the late stage of the disease, the active drug should be able to pass blood–brain barrier. Analyses of central nervous system (CNS) drugs [5,6] showed CNS drugs have molecular weight (MW) in the range from 141 to 452, clogP from −0.66 to 6.1 and topological polar surface area (tPSA) from 3.2 to 97 Å^2. Combined analyses of CNS drugs and drug candidates have provided guidelines on these physico-chemical properties [5,6], such as $250 < MW < 355$, $1.5 < clogP < 2.7$, and $25 < tPSA < 60$. In this paper we present a synthetic route to convolutamine I (**1**) and a series of analogues designed to lower MW, clogP and keep tPSA in the CNS drug range while maintaining activity.

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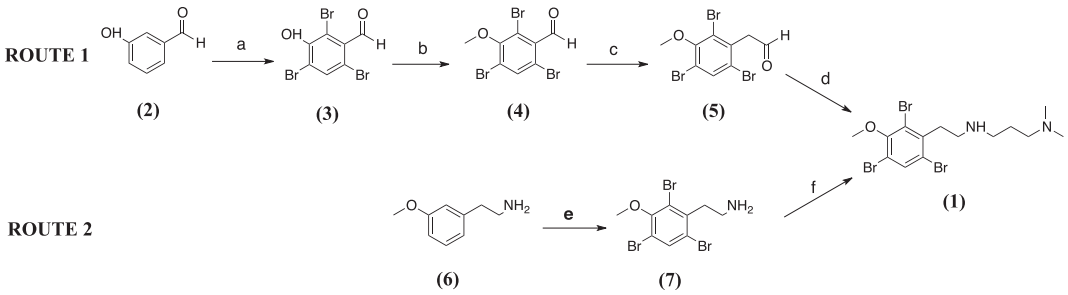


Scheme 1. Synthesis of **1**. Reagent and conditions: (a) Br_2, H_2O, rt, 3 days, 65% yield; (b) MeI, K_2CO_3, DMF, rt, 65% yield; (c) (i) $ClCH_2COOEt$, NaOEt, dry toluene, (ii) NaOH 30%, (iii) HCl con., reflux, 13% yield; (d) $NH_2(CH_2)_3NMe_2$, $NaBH_4$/K10, microwave, 10 min, 56% yield, (e) Br_2, AcOH/HCl, 80 °C, 85% yield; (f) 3-chloro-*N*,*N*-dimethylpropan-1-amine, H_2O/CH_2Cl_2, 140 °C, 10 min, 60% yield.

2. Results and discussion

2.1. Chemistry

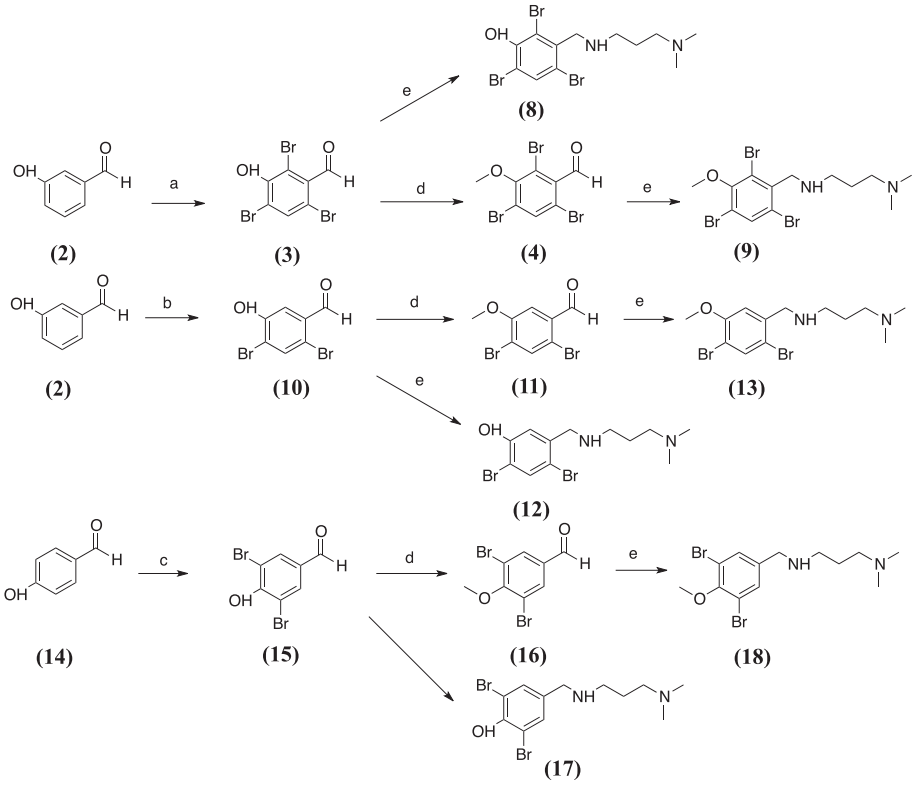
Convolutamine I (**1**) was synthesized by two different routes in order to facilitate analogue development. In the first route, 3-hydroxybenzaldehyde (**2**) was brominated [7] to give the brominated aldehyde (**3**) that was then treated with methyl iodide in DMF in the presence of K_2CO_3 to give the methoxy brominated benzaldehyde (**4**). Carbon–carbon elongation of **4** was performed *via* Darzens condensation to give **5** which was subsequently condensed with N^1,N^1-dimethylpropane-1,3-diamine in the presence of mixture of $NaBH_4$ and clay K10 under microwave irradiation [8] to give **1** (Route 1, Scheme 1).

In the second synthetic route, 3-methoxy phenylethanamine (**6**) was brominated in the presence of bromine in acetic acid to give the 2-,4-,6-tribromo derivative (**7**). A dimethylaminoethyl side chain was introduced to **7** by an N-alkylation reaction [9] with alkyl chloride to give convolutamine I (**1**) (Route 2, Scheme 1). NMR data of **1** was consistent with the isolated natural product [4].

Analogues **8**, **9**, **12**, **13**, **17**, **18** with a one carbon shorter chain between the phenyl group and the first nitrogen compared to **1** were synthesized by brominating 3-hydroxybenzaldehyde or 4-hydroxybenzaldehyde and condensation with N^1,N^1-dimethylpropane-1,3-diamine according to Scheme 2. Compounds **19**–**22** (Table 1) were synthesized in an analogous route without the bromination step. The carbon NMR data for this series with 11 distinct signals confirmed one carbon shorter in the side chain of these analogues. Compounds **8** and **9** had (+)-LRESIMS 1:3:3:1 cluster of ions indicative of 3 bromine atoms. **8** and **9** had one aromatic proton signal at δ_H 7.60 and 7.96, respectively, and three upfield quaternary carbon signals at 105–120 ppm, confirming a three-bromine-substituted aromatic ring. Compounds **12** and **13** had two singlet aromatic protons *para* to each other at δ_H 7.53, 6.86 and 7.73, 7.21, respectively, and two diagnostic quaternary brominated carbon signals at δ_C 105–120, confirming a 2,4-dibromo substituted aromatic ring. Compound **18** had one aromatic signal at δ_H 7.63 assigned to 2 eq. protons; its attached carbon had a chemical shift of δ_C 133.8, confirming a 2,5-dibromo-4-methoxy substituted aromatic ring.

Analogues with 2 bromine substituents (**25**, **26**) or no bromine (**29**) were synthesized following the reaction sequence of Scheme 2. To achieve a 2 bromine-substituted phenethylamine, a less acidic condition and a lower reaction temperature (60 °C) were used (Scheme 3). The intermediates **23** and **24** were used as a mixture in the N-alkylation step. The mixture of products **25** and **26** was purified and separated by reversed-phase HPLC. All final compounds and intermediates were fully characterized by the usual spectroscopic methods (see Experimental section). The (+)-LRESIMS of **25** revealed a 1:3:1 cluster of ions at *m*/*z* 393/395/397 $[M + H]^+$, indicative of two bromine atoms. The ^1H NMR spectrum of **25** shows two aromatic protons at δ_H 7.65 (s, 1H) and 6.78 (s, 1H), a methoxyl signal at 3.84 (s, 3H), a triplet–pentet–triplet pattern for the 1,3-disubstituted propane unit (NHR–CH_2–CH_2–CH_2–N(Me)$_2$) at δ_H 2.27 (t, J = 7.2 Hz, 2H), 1.65 (p, J = 7.1 Hz, 2H) and 2.67 (t, J = 7.1 Hz, 2H), a four proton multiplet for the di-substituted ethane unit at δ_H 2.84–2.86 (m, 4H), and an N-methyl signal for 2 eq. methyl groups at δ_H 2.17 (6H, s). The g-COSY correlations confirm the assignment of the δ_H 2.27, 1.65, 2.67 to the NHR–CH_2–CH_2–CH_2–N$(CH_3)_2$ substructure. The HSQC allows the assignment of all protons to their directly attached carbons, confirming one aromatic proton flanked by two bromine atoms with a downfield proton chemical shift (δ_H 7.65) and a downfield carbon chemical shift for its attached carbon (δ_C 136.2). The structure elucidation for **25** is completed with HMBC correlations of the 2 eq. N-methyl groups at δ_H 2.17 (s, 6H) to the terminal carbon (δ_C 58.0) of the propane unit (NHR–CH_2–CH_2–**C**H_2–N$(CH_3)_2$), the proton of propane unit (δ_H 2.67) to the second carbon (δ_C 49.4) of the ethane unit and the proton of the ethane unit (δ_H 2.86) to carbons (δ_C 139.9, 115.0 and 113.9) of the aromatic ring. Compound **26** was distinguished from **25** by the two aromatic proton signals at δ_H 7.47 and 6.67 with a typical coupling constant of 8.8 Hz for two adjacent aromatic protons. The carbon bearing the proton δ_H 6.67 had the chemical shift of δ_C 111.2, confirming its position being adjacent to the methoxy bearing carbon and 2,6-dibromo substitutions in the aromatic ring.

The alkylation reactions were first performed in NaH/DMF or THF, however this led to multi-alkylated products rather than mono-alkylated products. Milder basic conditions such as triethylamine in chloroform/ethanol [10], or $NaHCO_3$, SDS in water at 80 °C [11], or Cs_2CO_3 in DMF at rt [12], failed to produce products. In the past few years, microwave assisted reactions have been employed and have successfully delivered high yield, clean products with short reaction times. The efficiency of microwave irradiation over the conventional thermal process lies in its uniform heat delivery to all reactants in a closed reaction vessel. Monitored with LC–UV–MS for the formation of convolutamine I (**1**), the N-alkylation reaction gave the best yield in water/chloroform at 70:30 or 90:10 ratio depending on water solubility of reagents, at pH10 using sodium hydroxide 2 M, and a microwave temperature at 140 °C for 10 min. We also found that product yield was the same if we used sodium hydroxide or triethylamine for pH adjustment, however the partition purification step was more efficient if sodium hydroxide was used. Under these optimized conditions, mono-alkylated and di-alkylated products were obtained in a ratio of 2:1 or 3:1 (mono-alkylation:di-alkylation) while tri-alkylated amines were not formed as monitored by LC–UV–MS. If the reaction temperature was increased to 150 °C or 160 °C, the percentage of di-alkylated product was also increased.



Scheme 2. Synthesis of **8**–**18**. Reagent and conditions: a) Br_2, AcOH/HCl, 80 °C, 85% yield; (b) Br_2, $CHCl_3$, rt, 3 days, 70% yield; (c) Br_2, AcONa/AcOH, rt, 1 h, 90% yield; (d) MeI, K_2CO_3, DMF, rt, 46–93% yield; (e) $NH_2(CH_2)_3NMe_2$, $NaBH_4$/K10, microwave, 10 min, 56–75% yield.

Compound **30** was synthesized *via* N-alkylation of **25** with 3-chloroprop-1-yne under microwave irradiation. Compound **31** was synthesized by reacting **25** with acetyl chloride in chloroform basified with NaOH. Analogues without the nitrogen terminal group (**32**–**35**) were synthesized using an N-alkylation of intermediate brominated phenethylamine **23**. Compound **36** was a cyclization product of the N-alkylation reaction of **23** and 4-chlorobut-1-yne under microwave irradiation at 200 °C for 15 min. Compounds with different ring systems were synthesized in the same reaction sequence as in Scheme 2. Commercial 2-(naphthalen-2-yl)ethanamine, 2-(pyridin-3-yl)ethanamine, 2-(thiophen-2-yl)ethanamine, (2,3-dihydro-1*H*-inden-2-yl)methanamine were treated with 3-chloro-*N*,*N*-dimethylpropan-1-amine to give **37**–**40**. A series of analogues with different substituted groups on the phenyl group were synthesized in the same reaction sequence as in Scheme 2 to give **27**–**29**, **41**–**55** (Fig. 1).

2.2. Anti-trypanosomal activity

The anti-trypanosomal activity of **1**, **8**, **9**, **12**, **13**, **17**–**22**, **25**–**55** was evaluated *in vitro* against *T. b. brucei* (Table 1). Synthetic convolutamine I (**1**) exhibited potent activity against *T. b. brucei* with an IC_{50} value of 1.1 μM, comparable to the isolated convolutamine I.

Compounds **8**, **9**, **12**, **13**, **17**–**22** examined the importance of the length between the phenyl group and the first nitrogen of the side chain of convolutamine I in parallel with the importance of bromine substitution. Reducing the 2-carbon chain in **1** to a 1-carbon chain led to a loss of activity for tri-brominated **9**, but retained the activity for di-brominated **12**, **13**. Removal of all bromine atoms and replacing the methoxy with a hydroxy group (**19**, **20**) or retaining the methoxy group (**21**, **22**) gave a loss in activity. 4-Methoxy/hydroxy 3,5-dibromo compounds (**17**–**18**) had a loss of activity, indicating that bromine atoms at positions C-4 and C-6 are important.

Compounds **25**–**29** investigated the importance of bromine atom at position C-2, C-4 and C-6 for analogues having a 2-carbon side chain between the phenyl group and the first nitrogen. Results showed that **25**, with a loss of a bromine atom at C-2, displayed an increase in activity (IC_{50} 0.3 μM). A complete removal of bromine atoms resulted in a loss of activity (**29**). Other rearrangements of bromine and methoxy groups on the phenyl group were not effective in retaining activity. As activity was retained by removing the bromine at C-2, this substitution was retained in the next series of analogues.

An acetamide or a propyne attached to the first nitrogen aimed at a reduction of basicity (**30**, **31**) led to a loss of activity. Replacing the second basic terminal nitrogen with a non-basic terminal group such as a hydroxy (**33**), or other terminal alkyne groups (**34**, **35**) led to a loss of activity. However, replacement with a $-NH_2$ group (**32**) retained activity (IC_{50} 2 μM). The result suggested the side chain terminal group should be basic. The result supported the finding in our previous published paper [3] that the terminal tetrahydropyrimidinium group of the side chain in convolutamine J caused reduction in activity (IC_{50} 13.6 μM). Replacing the brominated phenyl group by naphthalene, pyridine, thiophene and 2,3-dihydro-1*H*-inden-2-amine (**37**–**40**) also gave a loss of activity, suggesting a phenyl group with large electrophilic substitutes was important.

These results established that the phenyl group and the side chain containing 2 basic nitrogen atoms were all important. We then conducted a series of analogues (**41**–**55**) with other halogen-substituted phenyl groups in place of the non drug-like tri- or di-brominated phenyl group. Walking a bromine atom or a fluorine atom around the phenyl group produced a loss of activity (**41**–**46**).

Table 1
Anti-trypanosomal activity.

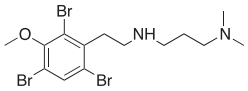
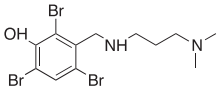
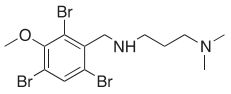
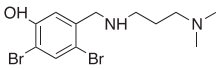
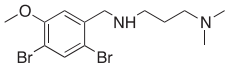
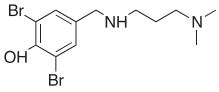
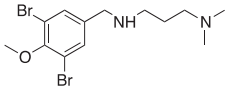
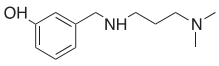
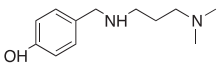
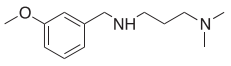
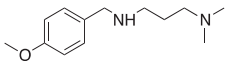
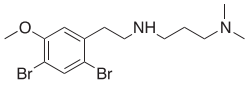
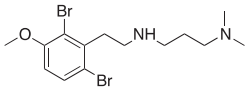
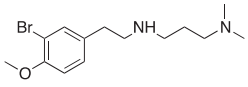
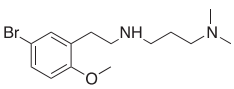
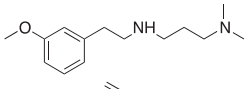
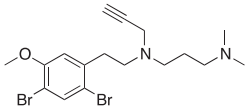
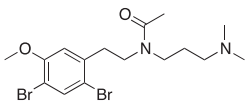
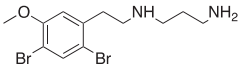
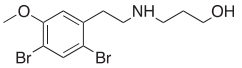
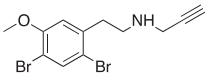
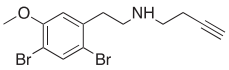
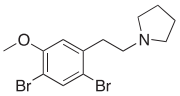
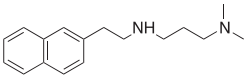
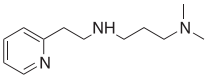
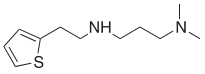
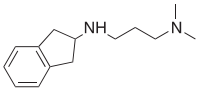
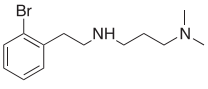
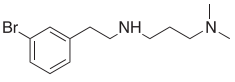
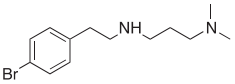
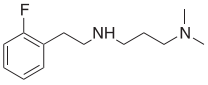
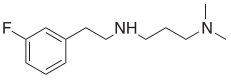
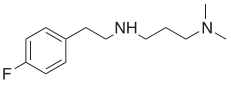
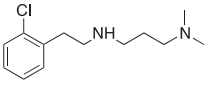
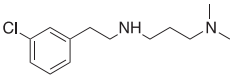
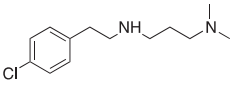
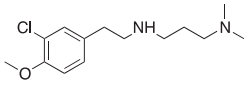
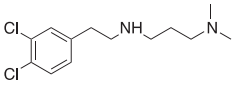
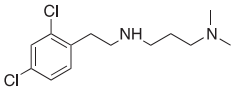
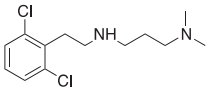
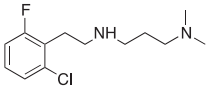
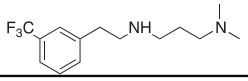
Compound	Structure	Activity (IC_{50} μM)	MW	clogP	tPSA
1		1.1	473.0	4.05	24.50
8		>8	445.0	2.30	35.50
9		>8	459.0	3.76	24.50
12		2.2	366.1	1.49	35.50
13		4.6	380.1	2.99	24.50
17		>8	366.1	1.65	35.50
18		>8	380.1	2.99	24.5
19		>8	208.3	0.42	35.50
20		>8	208.3	0.40	35.50
21		>8	222.3	1.45	24.50
22		>8	222.3	1.45	24.50
25		0.3	394.1	3.2	24.5
26		4-8	394.1	3.28	24.50
27		>8	315.2	2.51	24.50
28		>8	315.2	2.51	24.50
29		>8	236.3	1.74	24.50
30		>8	432.2	3.89	15.71
31		>8	436.2	2.89	32.78

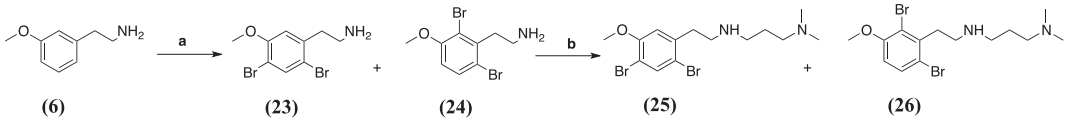
Table 1 (*continued*)

Compound	Structure	Activity (IC_{50} μM)	MW	clogP	tPSA
32		2.0	366.1	2.46	47.28
33		>8	367.1	2.57	41.49
34		>8	347.0	3.43	21.26
35		>8	361.1	3.72	21.26
36		>8	363.1	3.99	12.47
37		4–8	256.4	2.89	15.27
38		>8	207.3	0.71	28.16
39		>8	212.3	1.81	15.27
40		>8	218.3	2.00	15.27
41		>8	285.2	2.67	15.27
42		>8	285.2	2.67	15.27
43		>8	285.2	2.67	15.27
44		>8	224.3	1.66	24.06
45		>8	224.3	1.66	24.06
46		>8	224.3	1.66	24.06
47		>8	240.7	2.50	15.27
48		0.7	240.7	2.50	15.27
49		>8	240.7	2.50	15.27

(*continued on next page*)

Table 1 (*continued*)

Compound	Structure	Activity (IC_{50} μM)	MW	clogP	tPSA
50		>8	270.8	2.35	24.50
51		>8	275.2	3.11	15.27
52		>8	275.2	3.11	15.27
53		>8	275.2	3.11	15.27
54		>8	258.8	2.65	15.27
55		0.5	274.3	2.78	15.27



Scheme 3. Synthesis of **25**, **26**. Reagent and conditions: (a) Br_2, AcOH, 60 °C, 2 h, 85% yield; (b) 3-chloro-*N*,*N*-dimethylpropan-1-amine, H_2O/CH_2Cl_2, pH10, 140 °C, 10 min, 60% yield.

However, a chlorine atom at C-3 (**48**) retained activity (IC_{50} 0.7 μM) while a chlorine atom at C-2 (**49**) or C-4 (**50**) produced loss of activity. Since compound **48** with one chlorine atom gave comparable activity to compound **25** and convolutamine I (**1**), the next series of analogues was made having 2 chlorine atoms or a combination of 1 chlorine and a methoxy group (**50**–**53**). The result showed that more than one chlorine atom was unfavourable to activity.

Since a chlorine substituent a C-3 (**48**) was important, we replaced the chlorine with a trifluoromethyl group (**55**) to explore if this modification improves the biological properties. During the past twenty years a substantial effort has been devoted to the incorporation of the trifluoromethyl group into prototype molecules due to its known unique chemical and physiological stability. In most instances, the trifluoromethyl group has been used to replace a methyl group or a chlorine atom. The main advantage of trifluoromethyl-substituted aryl compounds is the ability to increase lipid solubility and thereby enhance the rate of absorption and transport of the drug across the blood–brain barrier [13]. Compound **55** had an IC_{50} of 0.5 μM, which was as potent as **48** and two-fold more active than the natural product convolutamine I (**1**).

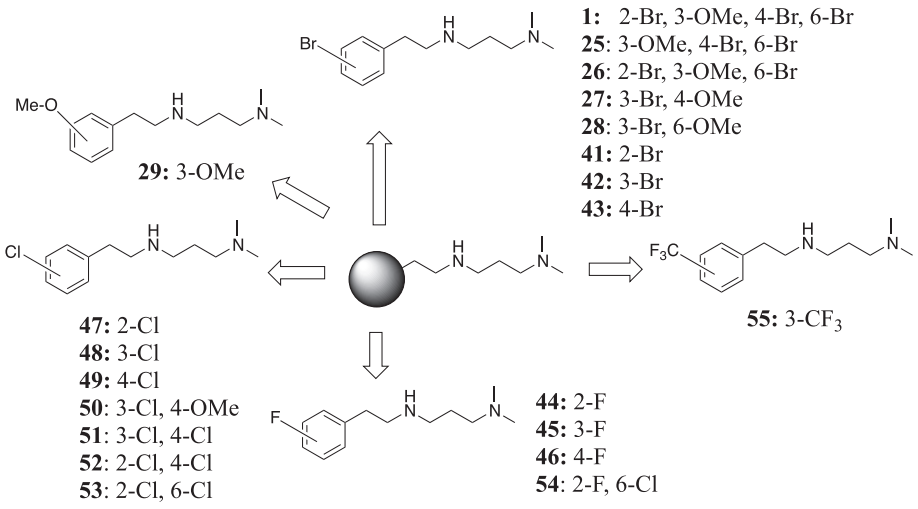


Fig. 1. Different halogen substitutions on the phenyl group of **1**, **25**–**29** and **41**–**55**.

Compounds **48** and **55** had MW of 240.7 and 274.3 and clogP of 2.50 and 2.78 respectively, compared with the natural product MW of 473.0, clogP of 4.05. Compounds **48** and **55** had physico-chemical properties in the region of CNS drugs [5]. Their MW, clogP and tPSA values were close to the preferred lower limit for CNS drugs (MW at 250, clogP at 2.1 and tPSA at 23) [5]. The structure–activity study emphasized the importance of the basicity of the nitrogen in the side chain (Fig. 2) and demonstrated a great improvement on compound properties since the new active compounds have a much lower molecular weight, and better log *P* values and may allow further analogue development.

3. Conclusion

We have identified lead anti-trypanosoma compounds **48** and **55**, which have low micromolar activity. Compounds **48** and **55** have improved drug-like properties compared with the lead natural product convolutamine I (**1**). The improvements in the drug-like profile of **48** and **55** are attributed to the replacement of 3 bromines and one methoxy with a chlorine atom or a trifluoromethyl group. The structure–activity relationships established in the course of designing **48** and **55** may be usefully applied for future design strategies for potent and drug-like compounds from brominated natural products.

4. Experimental protocols

4.1. General

NMR spectra were recorded at 30 °C on a Varian Inova 600 MHz and 500 MHz spectrometers. The ^{1}H and ^{13}C chemical shift were referenced to the CD_3OD solvent peaks at δ_H 4.80 and δ_C 48.1 ppm, $CDCl_3$ solvent peaks at δ_H 7.26 and δ_C 77.0 ppm. Standard parameters were used for the 2D-NMR spectra obtained, which included g-COSY, gHSQC ($^{1}J_{CH}$ = 140 Hz), gHMBC ($^{n}J_{CH}$ = 8.3 Hz). Mass spectra were acquired using a Waters ZQ. High-resolution mass measurement was acquired on a Bruker Daltonics Apex III 4.7e Fourier transform mass spectrometer, fitted with an Apollo API source. A Betasil C_{18} column (5 μm, 150 × 21.2 mm) and Hypersil BDS C_{18} column (5 μm, 250 × 10 mm) were used for semi-preparative HPLC. A Phenomenex Luna C_{18} column (3 μm, 4.6 × 50 mm) was used for LC/MS controlled by MassLynx 4.1 software. All solvents used for chromatography were Omnisolv HPLC grade and the H_2O used was Millipore Milli-Q PF filtered. All the starting amines and alkyl halides were obtained from Aldrich Chemical Co. and were used as such.

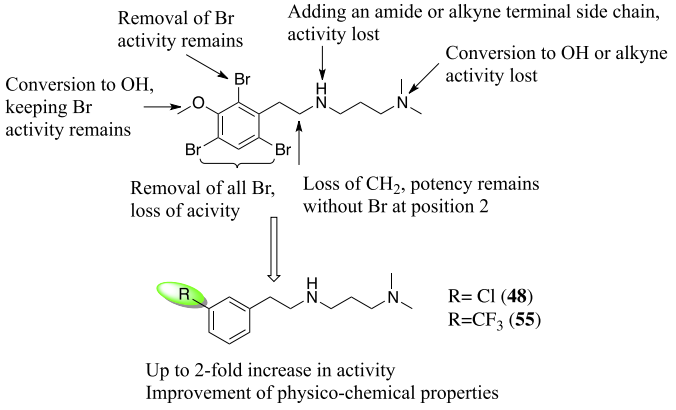


Fig. 2. Structure–activity relationship study of **1**.

4.2. Activity assay – IC_{50} measurement

IC_{50}s were determined according to Sykes and Avery [14] with some modifications. Briefly, a starting inoculum of 2 × 10^3 *T. b. brucei* 427 bloodstream form parasites were incubated with a range of two-fold serial dilutions drug concentrations in 96-well culture plates, in a final volume of 200 μL per well (HMI-9 with 10% FBS), for 48-h at 37 °C–5% CO_2. 20 μL of Alamar Blue™ was then added to each well before an additional 4-h incubation in the same culture conditions. Positive control (parasites in absence of drug) and negative control (absence of both parasites and drug) culture conditions were included in each plate. Fluorescence signal was quantified using SpectraMax M2 Multi-mode plate Reader (Ext: 544 – Em: 590). IC_{50} values were determined using the GraphPad Prism5 software. Compounds were tested with three biological replicates and the value of each biological replicate is the average of three technical replicates.

4.3. Typical procedure for bromination reaction

To a cooled solution (5 °C) of 3-hydroxybenzaldehyde (0.409 mmol, 0.500 g) in glacial acetic acid (8.0 mL, 0.14 mol), Br_2 (0.12 mL, 2.3 mmol) was added and stirred for 3 h at r.t. After completion of the reaction, the reaction was quenched with saturated $Na_2S_2O_3$ solution and the solvent was removed under vacuum pressure. The reaction mass was then extracted with ethyl acetate. The organic layer was dried prior to being purified by RP-HPLC column to give brominated compounds.

4.4. Typical procedure for reductive amination reaction (microwave irradiation)

In a 0.5–2 mL microwave vial were added 5 mg of clay K10, 2,4,6-tribromo-3-methoxy-benzaldehyde (12 mg, 0.031 mmol, 1 eq.), *N,N*-dimethyl 1,3-propane diamine (4 μL, 0.031 mmol, 1 eq.) and 100 μL of MeOH. The mixture was stirred for 2 min, sealed and then irradiated for 10 min at 65 °C. A mixture of 5 mg of clay K10 with sodium borohydride 95% (1.25 mg, 0.031 mmol, 1 eq.) was then added to the reaction mixture, it was sealed and irradiated for 5 min at 100 °C. It was then diluted with MeOH, filtered, concentrated to dryness and purified by Flash chromatography (silica gel, DCM/MeOH/NEt_3 80/20/0.01) to give **1** (8.5 mg, 58% yield).

4.5. Typical procedure for reductive amination reaction

To a stirred solution of 4-methoxy-benzaldehyde (100 mg, 0.734 mmol, 1 eq.) and *N,N*-dimethyl 1,3-propane diamine (102 μL, 0.808 mmol, 1.1 eq.) in 2 mL of dry DCM was added a small spatula of Na_2SO_4. The resulting mixture was stirred at room temperature for 22 h. When there is no evidence of starting material by TLC, the reaction mixture was filtered and concentrated to dryness. It was then dissolved in MeOH (1 mL) and sodium borohydride 95% (15 mg, 0.367, 0.5 eq.) was added. The reaction mixture was stirred at room temperature for 96 h and was then concentrated to dryness and purified by flash chromatography (silica gel, EtOAc/MeOH/NEt_3 90/10/0.1 to 50/50/0.1) to give **22** (45.7 mg, 28% yield).

4.6. Typical procedure for N-alkylation

A mixture of substituted phenylethanamine (0.1 mmol), alkyl chloride (0.12 mmol) in a water–chloroform (70:30, 0.5 mL) and NaOH in water to reach pH10 (2 M solution) was placed in a microwave tube (2 mL). The tube was subjected to MW irradiation at 140 °C for 10 min. After completion of the reaction (monitored by LC/MS), the product was extracted into ethyl acetate. Removal of

the solvent under reduced pressure, followed by reversed-phase HPLC chromatography using water–methanol as eluent in a gradient system for 60 min afforded final product and confirmed by satisfactory ^{1}H and ^{13}C or 2D (g-COSY, HSQC, HMBC) NMR spectra.

4.7. Synthesis of target compounds

4.7.1. N^1,N^1-Dimethyl-N^3-(2,4,6-tribromo-3-methoxyphenethyl) propane-1,3-diamine (**1**)

Obtained as a yellow oil, 3% yield (synthetic route 1), 50% yield (synthetic route 2); ^{1}H (600 MHz, DMSO-d_6) δ_H 7.96 (s, 1H), 3.78 (s, 3H), 3.04 (m, 2H), 2.63 (m, 2H), 2.56 (m, 2H), 2.22 (m, 2H), 2.09 (s, 6H), 1.52 (t, J = 7.5 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) 154.2, 140.8, 135.8, 120.5, 120.0, 115.9, 61.0, 58.2, 48.0, 48.1, 46.1 (×2), 38.3, 28.3. HRESIMS(+): m/z calculated for $[C_{14}H_{22}N_2O_1Br_3]^+$ 470.9276, found 470.9267.

4.7.2. N^1,N^1-Dimethyl-N^3-(2,4,6-tribromo-3-methoxybenzyl) propane-1,3-diamine (**8**)

Obtained as a yellow oil, 60% yield; ^{1}H (500 MHz, CD_3OD) δ_H 7.60 (s, 1H), 4.19 (s, 2H), 2.99 (m, 2H), 2.85 (m, 2H), 2.56 (s, 6H), 1.87 (t, J = 7.5 Hz, 2H), ^{13}C NMR (125 MHz, CD_3OD) 161.5, 135.0, 135.0, 119.6, 116.1, 106.0, 59.4, 54.3, 48.5, 44.4 (×2), 24.8. HRESIMS(+): m/z calculated for $C_{12}H_{18}N_2O_1Br_3$ 442.8963 found 442.8966.

4.7.3. 2,4,6-Tribromo-3-(((3-(dimethylamino)propyl)amino) methyl)phenol (**9**)

Obtained as a yellow oil, 59% yield; ^{1}H (500 MHz, CD_3OD) δ_H 7.96 (s, 1H), 4.17 (s, 2H), 3.93 (s, 3H), 2.77 (m, 2H), 2.56 (m, 2H), 2.37 (s, 6H), 1.80 (t, J = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, CD_3OD) 155.6, 140.5, 136.9, 123.3, 121.3, 118.4, 61.1, 58.9, 54.3, 48.5, 45.3 (×2), 27.7. HRESIMS(+): m/z calculated for $C_{13}H_{20}N_2O_1Br_3$ 456.9120 found 456.9126.

4.7.4. 2,4-Dibromo-5-(((3-(dimethylamino)propyl)amino)methyl) phenol (**12**)

Obtained as a yellow solid, 47% yield; ^{1}H (500 MHz, CD_3OD) δ_H 7.53 (s, 1H), 6.86 (s, 1H), 3.70 (s, 2H), 2.66 (t, J = 7.5 Hz, 2H), 2.44 (t, J = 7.5 Hz, 2H), 2.26 (s, 6H), 1.75 (p, J = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, CD_3OD) 159.2, 138.6, 136.4, 120.5, 112.5, 110.3, 58.7, 53.6, 48.1, 45.2 (×2), 26.9. HRESIMS(+): m/z calculated $C_{12}H_{19}N_2O_1Br_2$ 364.9858, found 364.9864.

4.7.5. N^1-(2,4-Dibromo-5-methoxybenzyl)-N^3,N^3-dimethylpropane-1,3-diamine (**13**)

Obtained as a yellow solid, 48% yield; ^{1}H (500 MHz, CD_3OD) δ_H 7.73 (s, 1H), 7.21 (s, 1H), 3.91 (s, 3H), 3.85 (s, 2H), 2.69 (t, J = 7.5 Hz, 2H), 2.42 (t, J = 7.50 Hz, 2H), 2.27 (s, 6H), 1.78 (p, J = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, CD_3OD) 157.0, 140.6, 136.9, 115.0, 114.8, 111.6, 58.7, 57.0, 53.9, 48.2, 45.5 (×2), 28.1. HRESIMS(+): m/z calculated for $C_{13}H_{21}N_2O_1Br_2$ 379.0015 found 379.0019.

4.7.6. 2,6-Dibromo-4-(((3-(dimethylamino)propyl)amino)methyl) phenol (**17**)

Obtained as a yellow solid, 66% yield; ^{1}H (500 MHz, CD_3OD) δ_H 7.31 (s, 2H), 3.76 (s, 2H), 2.90 (m, 2H), 2.49 (m, 2H), 2.31 (s, 6H), 1.86 (p, J = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, CD_3OD) 161.0, 133.5 (×2), 120.5 (×2), 115.9, 58.4, 51.8, 47.5, 45.2 (×2), 25.0. HRESIMS(+): m/z calculated $[C_{12}H_{19}N_2O_1Br_2]^+$, 364.9858, found 364.9858.

4.7.7. N^1-(3,5-Dibromo-4-methoxybenzyl)-N^3,N^3-dimethylpropane-1,3-diamine (**18**)

Obtained as a yellow solid, 50% yield; ^{1}H (500 MHz, CD_3OD) δ_H 7.63 (s, 2H), 3.90 (s, 3H), 3.74 (s, 2H), 2.63 (m t, J = 7.5 Hz, 2H), 2.42 (t, J = 7.5 Hz, 2H, m), 2.30 (s, 6H), 1.75 (p, J = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, CD_3OD) 154.3, 140.2, 133.8 (×2), 118.8 (×2), 61.0, 58.6, 52.8, 48.0, 45.4 (×2), 28.0. HRESIMS(+): m/z calculated $[C_{13}H_{21}N_2O_1Br_2]^+$ 379.0015, found 379.0020.

4.7.8. 3-(((3-(Dimethylamino)propyl)amino)methyl)phenol (**19**)

Obtained as a yellow solid, 75% yield; ^{1}H (500 MHz, CD_3OD) δ_H 7.14 (t, J = 8.0 Hz, 1H), 6.77 (m, 2H), 6.69 (d, J = 8.0 Hz, 1H), 3.66 (s, 2H), 2.58 (m, 2H), 2.33 (m, 2H), 2.22 (s, 6H), 1.70 (p, J = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, CD_3OD) 159.0, 142.0, 130.4, 120.4, 116.5, 115.2, 58.7, 54.4, 48.1, 45.4 (×2), 27.9. HRESIMS(+): m/z calculated $[C_{12}H_{21}N_2O_1]^+$ 209.1648, found 209.1649.

4.7.9. 4-(((3-(Dimethylamino)propyl)amino)methyl)phenol (**20**)

Obtained as a yellow solid, 75% yield; ^{1}H (500 MHz, CD_3OD) δ_H 7.06 (dd, J = 8.5, 2.3 Hz, 2H), 6.67 (dd, J = 8.5, 2.3 Hz, 2H), 3.56 (s, 2H), 2.51 (t, J = 7.5 Hz, 2H), 2.26 (t, J = 7.5 Hz, 2H), 1.63 (p, J = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, CD_3OD) 157.8, 140.9, 129.4 (×2), 114.5 (×2), 57.2, 52.5, 46.6, 44.0 (×2), 26.5. HRESIMS(+): m/z calculated $[C_{12}H_{21}N_2O_1]^+$ 209.1648, found 209.1649.

4.7.10. N^1-(3-Methoxybenzyl)-N^3,N^3-dimethylpropane-1,3-diamine (**21**)

Obtained as a yellow solid, 66% yield; ^{1}H (500 MHz, CD_3OD) δ_H 7.25 (t, J = 8.0 Hz, 1H), 6.95 (s, 1H), 6.92 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 2H), 2.63 (m, 2H), 2.38 (m, 2H), 2.26 (s, 6H), 1.73 (t, J = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, CD_3OD) 161.3, 141.9, 130.5, 121.7, 115.0, 113.8 58.7, 55.6, 54.3, 48.1, 45.4 (×2), 27.8. HRESIMS(+): m/z calculated $[C_{13}H_{23}N_2O_1]^+$ 223.1805, found 223.1806.

4.7.11. N^1-(4-Methoxybenzyl)-N^3,N^3-dimethylpropane-1,3-diamine (**22**)

Obtained as a yellow solid, 28% yield; ^{1}H (500 MHz, CD_3OD) δ_H 7.29 (d, J = 8.5 Hz, 2H), 6.92 (d, J = 8.5 Hz, 2H), 3.81 (s, 3H), 3.71 (s, 2H), 2.62 (t, J = 7.5 Hz, 2H), 2.38 (t, J = 7.5 Hz, 2H), 2.26 (s, 6H), 1.74 (p, J = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, CD_3OD) 160.3, 132.7, 130.7, 114.8, 58.7, 55.7, 53.9, 48.0, 45.4 (×2), 28.0. HRESIMS(+): m/z calculated $[C_{13}H_{23}N_2O_1]^+$ 223.1805, found 223.1805.

4.7.12. N^1-(2,4-Dibromo-5-methoxyphenethyl)-N^3,N^3-dimethylpropane-1,3-diamine (**25**)

Obtained as a yellow solid, 40% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.65 (s, 1H), 6.78 (s, 1H), 3.84 (s, 3H), 2.86 (m, 2H), 2.84 (m, 2H), 2.67 (t, J = 7.1 Hz, 2H), 2.27 (t, J = 7.2 Hz, 2H), 2.17 (s, 6H), 1.65 (p, J = 7.1 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) 155.3, 139.9, 136.2, 115.0, 113.9, 110.0, 56.4, 36.9, 49.4, 48.3, 58.0, 45.5 (×2), 28.0. HRESIMS(+): m/z calculated $[C_{14}H_{23}N_2O_1Br_2]^+$ 393.0171, found 393.0172.

4.7.13. N^1-(2,6-Dibromo-3-methoxyphenethyl)-N^3,N^3-dimethylpropane-1,3-diamine (**26**)

Obtained as a yellow solid, 30% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.47 (d, J = 8.8 Hz, 1H), 6.67 (d, J = 8.8 Hz, 1H), 3.88 (s, 3H), 3.28 (tb, 2H), 2.87 (tb, 2H), 2.82 (tb, 2H), 2.40 (tb, 2H), 2.25 (s, 6H), 1.74 (tb, 2H), ^{13}C NMR (150 MHz, $CDCl_3$) 155.8, 139.9, 132.1, 115.9, 115.2, 111.2, 58.4, 55.6, 48.1, 48.0, 45.3 (×2), 37.8, 27.6. HRESIMS(+): m/z calculated $[C_{14}H_{23}N_2O_1Br_2]^+$ 393.0171, found 393.0174.

4.7.14. N^1-(3-Bromo-4-methoxyphenethyl)-N^3,N^3-dimethylpropane-1,3-diamine (**27**)

Obtained as a yellow solid, 60% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.38 (s, 1H), 7.10 (d, J = 8.0 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 3.86 (s, 3H), 2.82 (t, J = 7.1 Hz, 2H), 2.71 (t, J = 7.1 Hz, 2H), 2.64 (t, J = 7.2 Hz, 2H), 2.27 (t, J = 7.2 Hz, 2H), 2.18 (s, 6H), 1.63 (p, J = 7.2 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) 154.4, 134.0, 133.5, 128.8, 112.1, 111.7, 58.2,

56.4, 51.2, 48.4, 45.6 (×2), 35.2, 28.1. HRESIMS(+): *m*/*z* calculated $[C_{14}H_{24}N_2O_1Br]^+$ 315.1066, found 315.1063.

4.7.15. N^1-(5-Bromo-2-methoxyphenethyl)-N^3,N^3-dimethylpropane-1,3-diamine (**28**)

Obtained as a yellow solid, 65% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.28 (s, 1H), 7.25 (dd, J = 8.5, 1.2 Hz, 1H), 6.70 (dd, J = 8.5, 1.2 Hz, 1H), 2.81 (d, J = 6.6 Hz, 2H), 2.77 (d, J = 6.6 Hz, 2H), 2.65 (t, J = 7.1 Hz, 2H), 2.28 (t, J = 7.1 Hz, 2H), 2.19 (s, 6H), 1.64 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) 156.9, 133.0, 131.1, 130.1, 112.7, 112.2, 58.2, 55.7, 49.6, 48.3, 45.7 (×2), 30.8, 28.2. HRESIMS(+): *m*/*z* calculated $[C_{14}H_{24}N_2O_1Br]^+$ 315.1066, found 315.1068.

4.7.16. N^1-(3-Methoxyphenethyl)-N^3,N^3-dimethylpropane-1,3-diamine (**29**)

Obtained as a yellow solid, 57% yield; ^{1}H (500 MHz, CD_3OD) δ_H δ 7.26 (t, J = 8.0 Hz, 1H), 6.94 (m, 3H), 3.84 (s, 3H), 2.90 (m, 2H), 2.84 (m, 2H), 2.71 (t, J = 7.5 Hz, 2H), 2.39 (t, J = 7.5 Hz, 2H), 2.26 (s, 6H), 1.74 (p, J = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, CD_3OD) 160.3, 140.6, 129.3, 120.6, 114.1, 111.4, 57.4, 54.2, 50.1, 47.4, 43.8 (×2), 34.7, 25.5. HRESIMS(+): *m*/*z* calculated $[C_{14}H_{25}N_2O_1]^+$, 237.1961, found 237.1965.

4.7.17. N^1-(2,4-Dibromo-5-methoxyphenethyl)-N^3,N^3-dimethyl-N^1-(prop-2-yn-1-yl)propane-1,3-diamine (**30**)

Obtained as a yellow solid, 35% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.67 (s, 1H), 6.80 (s, 1H), 3.87 (s, 3H), 3.42 (s, 2H), 2.85 (t, J = 7.4 Hz, 2H), 2.74 (t, J = 7.4 Hz, 2H), 2.59 (t, J = 7.3 Hz, 2H), 2.27 (t, J = 7.4 Hz, 2H), 2.21 (s, 6H), 1.63 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) 155.3, 140.0, 136.4, 115.0, 113.9, 109.8, 57.7, 56.4, 53.3, 51.6, 45.5 (×2), 42.1, 34.5, 25.7. HRESIMS(+): *m*/*z* calculated $[C_{17}H_{25}N_2O_1Br_2]^+$ 431.0328, found 431.0316.

4.7.18. N-(2,4-Dibromo-5-methoxyphenethyl)-N-(3-(dimethylamino)propyl)acetamide (**31**)

Obtained as a yellow solid, 35% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.69 (s, 1H), 6.97 (s, 1H), 3.93 (s, 3H), 3.55 (m, 4H), 3.00 (m, 4H), 2.79 (s, 6H), 2.16 (q, J = 7.5, 2H), 2.08 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) 171.6, 156.0, 137.4, 136.4, 114.9, 114.5, 111.4, 57.1, 56.4, 48.8, 43.6 (×2), 43.3, 35.8, 24.0, 21.7. HRESIMS(+): *m*/*z* calculated $[C_{16}H_{25}N_2O_2Br_2]^+$ 435.0277, found 435.0276.

4.7.19. N^1-(2,4-Dibromo-5-methoxyphenethyl)propane-1,3-diamine (**32**)

Obtained as a yellow solid, 60% yield; ^{1}H NMR (600 MHz, DMSO-d_6) δ_H 7.81 (s, 1H), 7.27 (s, 1H), 3.88 (s, 3H), 3.12 (m, 4H), 3.05 (t, J = 7.4 Hz, 2H), 2.93 (t, J = 7.4 Hz, 2H), 2.02 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) 155.0, 137.4, 135.0, 114.9, 114.5, 110.1, 56.4, 45.6, 31.5, 43.7, 35.9, 23.4. HRESIMS(+): *m*/*z* calculated $[C_{12}H_{19}N_2O_1Br_2]^+$ 364.9858, found 364.9859.

4.7.20. 3-((2,4-Dibromo-5-methoxyphenethyl)amino)propan-1-ol (**33**)

Obtained as a yellow solid, 70% yield; ^{1}H NMR (600 MHz, DMSO-d_6) δ_H 7.82 (s, 1H), 7.18 (s, 1H), 3.88 (s, 3H), 3.50 (t, J = 5.9 Hz, 2H), 3.17 (m, 4H), 3.05 (m, 2H), 3.04 (m, 2H), 1.78 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) 155.1, 136.6, 135.3, 114.8, 114.4, 109.9, 56.5, 57.8, 45.8, 31.6, 44.8, 28.5. HRESIMS(+): *m*/*z* calculated $[C_{12}H_{18}N_1O_2Br_2]^+$ 365.9698, found 365.9691.

4.7.21. N-(2,4-Dibromo-5-methoxyphenethyl)prop-2-yn-1-amine (**34**)

Obtained as a yellow solid, 55% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.69 (s, 1H), 6.82 (s, 1H), 3.88 (s, 3H), 3.48 (d, J = 2.4 Hz, 2H), 2.99 (t, J = 7.3 Hz, 2H), 2.91 (t, J = 7.3 Hz, 2H), 2.23 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) 155.5, 139.3, 136.4, 114.9, 114.0, 110.0, 81.6, 71.7, 56.5, 38.2, 48.1, 36.5. HRESIMS(+): *m*/*z* calculated $[C_{12}H_{14}N_1O_1Br_2]^+$ 345.9436, found 345.9423.

4.7.22. N-(2,4-Dibromo-5-methoxyphenethyl)but-3-yn-1-amine (**35**)

Obtained as a yellow solid, 50% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.68 (s, 1H), 6.80 (s, 1H), 3.87 (s, 3H), 2.89 (broad, 4H), 2.82 (t, J = 7.0 Hz, 2H), 2.40 (d, J = 7.0, 2.5 Hz, 2H), 1.97 (t, J = 2.5 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) 155.2, 139.7, 136.4, 115.0, 113.8, 109.2, 82.3, 69.5, 56.4, 48.5, 47.7, 36.8, 19.4. HRESIMS(+): *m*/*z* calculated $[C_{13}H_{16}N_1O_1Br_2]^+$ 359.9593, found 359.9593.

4.7.23. 1-(2,4-Dibromo-5-methoxyphenethyl)pyrrolidine (**36**)

Obtained as a yellow solid, 40% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.67 (s, 1H), 6.91 (s, 1H), 3.88 (s, 3H), 2.96 (m, 2H), 2.75 (m, 2H), 2.70 (m, 4H), 1.95 (t, broad, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) 155.7, 139.9, 136.4, 114.9, 114.2, 110.2, 56.7, 56.1, 53.7 (×2), 35.5, 23.6 (×2). HRESIMS(+): *m*/*z* calculated $[C_{13}H_{18}N_1O_1Br_2]^+$ 361.9749, found 361.9742.

4.7.24. N^1,N^1-Dimethyl-N^3-(2-(naphthalen-2-yl)ethyl)propane-1,3-diamine (**37**)

Obtained as a white solid, 70% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.79 (d, J = 8.1 Hz, 1H), 7.78 (d, J = 8.1 Hz, 2H), 7.65 (s, 1H), 7.45–7.41 (m, 2H) 7.35 (d, J = 8.1 Hz, 1H), 2.96 (m, 4H), 2.67 (t, J = 7.4 Hz, 2H), 2.26 (t, J = 7.4 Hz, 2H), 2.15 (s, 6H), 1.63 (p, J = 7.4 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) 137.7, 133.6, 133.1, 127.5 (×2), 127.1, 126.8 (×2), 125.7, 125.0, 57.8, 50.6, 47.9, 45.2 (×2), 36.2, 27.7. HRESIMS(+): *m*/*z* calculated $[C_{17}H_{25}N_2]^+$ 257.2012, found 257.2005.

4.7.25. N^1,N^1-Dimethyl-N^3-(2-(pyridin-3-yl)ethyl)propane-1,3-diamine (**38**)

Obtained as a pale yellow solid, 75% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.51 (d, J = 4.5 Hz, 1H), 7.57 (td, J = 7.7, 1.9 Hz, 1H), 7.15 (d, J = 7.7 Hz, 1H), 7.09 (dd, J = 4.5, 7.7 Hz, 1H), 2.97 (m, 4H), 2.65 (t, J = 7.3 Hz, 2H), 2.26 (t, J = 7.3 Hz, 2H), 2.17 (s, 6H), 1.62 (p, J = 7.3 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) 160.5, 149.4, 136.4, 123.4, 121.3, 58.1, 49.5, 48.3, 45.6 (×2), 38.6, 28.1. HRESIMS(+): *m*/*z* calculated $[C_{12}H_{22}N_3]^+$ 208.1808, found 208.1811.

4.7.26. N^1,N^1-Dimethyl-N^3-(2-(thiophen-2-yl)ethyl)propane-1,3-diamine (**39**)

Obtained as a yellow solid, 70% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.13 (d, J = 5.1 Hz, 1H), 6.92 (dd, J = 5.1, 3.5 Hz, 1H), 6.82 (J = 3.5 Hz, 1H), 3.02 (t, J = 6.9 Hz, 2H), 2.90 (t, J = 6.9 Hz, 2H), 2.67 (t, J = 7.1 Hz, 2H), 2.28 (t, J = 7.2 Hz, 2H), 2.19 (s, 6H), 1.64 (p, J = 7.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) 142.8, 126.9, 125.1, 123.6, 58.1, 51.3, 48.3, 45.6 (×2), 30.5, 28.1. HRESIMS(+): *m*/*z* calculated $[C_{11}H_{21}N_2S]^+$ 213.1419, found 213.1412.

4.7.27. N^1-((2,3-Dihydro-1H-inden-2-yl)methyl)-N^3,N^3-dimethylpropane-1,3-diamine (**40**)

Obtained as a yellow solid, 70% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.20 (m, 4H), 3.81 (tt, J = 6.8, 4.4 Hz, 1H), 3.31 (dd, J = 16.4, 6.7 Hz, 2H), 3.19 (dd, J = 16.3, 4.4 Hz, 2H), 3.12 (t, J = 6.0 Hz, 2H), 2.59 (t, J = 6.0 Hz, 2H), 2.15 (s, 6H), 1.98 (p, J = 6.0 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) 139.3(×2), 127.5 (×2), 125.1 (×2), 59.5, 58.5, 47.5, 44.7 (×2), 37.5 (×2), 22.7. HRESIMS(+): *m*/*z* calculated $[C_{14}H_{23}N_2]^+$ 219.1856, found 219.1848.

4.7.28. N^1-(2-Bromophenethyl)-N^3,N^3-dimethylpropane-1,3-diamine (**41**)

Obtained as yellow oil, 70% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.52 (d, J = 6 Hz, 1H), 7.25–7.20 (m, 2H), 7.06 (m, 1H), 2.93 (t,

J = 7.2 Hz, 2H), 2.87 (t, J = 7.2 Hz, 2H), 2.69 (t, J = 7.3 Hz, 2H), 2.29 (t, J = 7.3 Hz, 2H), 2.19 (s, 6H), 1.65 (ddd, J = 7.3 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) 139.7, 133.0, 130.9, 127.9, 127.5, 124.7, 58.2, 49.6, 48.3, 45.7 (×2), 36.9, 28.2. HRESIMS(+): m/z calculated $[C_{13}H_{22}N_2O_1Br]^+$ 285.0960, found 285.0958.

4.7.29. N^1-(3-Bromophenethyl)-N^3,N^3-dimethylpropane-1,3-diamine (**42**)

Obtained as yellow oil, 70% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.35 (s, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.16–7.11 (m, 2H), 2.85 (t, J = 7.1 Hz, 2H), 2.76 (t, J = 7.1 Hz, 2H), 2.65 (t, J = 7.0 Hz, 2H), 2.27 (t, J = 7.2 Hz, 2H), 2.18 (s, 6H), 1.62 (p, J = 7.1 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) 142.7, 131.9, 130.1, 129.4, 127.5, 122.6, 58.2, 51.0, 48.4, 45.6 (×2), 36.2, 28.1. HRESIMS(+): m/z calculated $[C_{13}H_{22}N_2O_1Br]^+$ 285.0960, found 285.0961.

4.7.30. N^1-(4-Bromophenethyl)-N^3,N^3-dimethylpropane-1,3-diamine (**43**)

Obtained as yellow oil, 60% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.40 (d, J = 8.1 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 2.83 (t, J = 7.2 Hz, 2H), 2.74 (t, J = 7.1 Hz, 2H), 2.64 (t, J = 7.1 Hz, 2H), 2.26 (t, J = 7.2 Hz, 2H), 2.17 (s, 6H), 1.63 (p, J = 7.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) 139.3, 131.6 (×2), 130.6 (×2), 120.0, 77.4, 76.9, 76.7, 58.1, 51.1, 48.4, 45.6 (×2), 35.9, 28.1. HRESIMS(+): m/z calculated $[C_{13}H_{22}N_2O_1Br]^+$ 285.0960, found 285.0959.

4.7.31. N^1-(2-Fluorophenethyl)-N^3,N^3-dimethylpropane-1,3-diamine (**44**)

Obtained as pale yellow oil, 70% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.23–7.15 (m, 2H), 7.05 (t, J = 7.5 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 2.85 (dq, J = 11.1, 5.6 Hz, 4H), 2.66 (t, J = 7.1 Hz, 2H), 2.28 (t, J = 7.1 Hz, 2H), 2.18 (s, 6H), 1.64 (p, J = 7.1 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) 162.2, 131.1, 128.0, 127.2, 124.1, 115.5, 58.1, 50.0, 48.3, 45.6 (×2), 29.9, 28.1. HRESIMS(+): m/z calculated $[C_{13}H_{22}F_1N_2]^+$ 225.1761, found 225.1752.

4.7.32. N^1-(3-Fluorophenethyl)-N^3,N^3-dimethylpropane-1,3-diamine (**45**)

Obtained as pale yellow oil, 75% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.23 (m, 1H), 6.97 (d, J = 7.5 Hz, 1H), 6.89 (m, 1H), 6.85 (m, 1H), 2.85 (t, J = 7.1 Hz, 2H), 2.78 (t, J = 7.1 Hz, 2H), 2.64 (t, J = 7.1 Hz, 2H), 2.26 (t, J = 7.1 Hz, 2H), 2.17 (s, 6H), 1.63 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) 163.9, 142.9, 130.0, 124.5, 115.7, 113.2, 58.1, 51.0, 48.4, 45.6 (×2), 36.2, 28.0. HRESIMS(+): m/z calculated $[C_{13}H_{22}F_1N_2]^+$ 225.1761, found 225.1752.

4.7.33. N^1-(4-Fluorophenethyl)-N^3,N^3-dimethylpropane-1,3-diamine (**46**)

Obtained as yellow oil, 70% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.15 (dd, J = 8.4, 5.6 Hz, 2H), 6.96 (t, J = 8.7 Hz, 2H), 2.83 (t, J = 7.4 Hz, 2H), 2.76 (t, J = 7.1 Hz, 2H), 2.64 (t, J = 7.1 Hz, 2H), 2.26 (t, J = 7.2 Hz, 2H), 2.17 (s, 6H), 1.62 (p, J = 7.1 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) 160.8, 135.9, 130.2 (×2), 115.4 (×2), 58.1, 51.4, 48.4, 45.6 (×2), 35.7, 28.1. HRESIMS(+): m/z calculated $[C_{13}H_{22}F_1N_2]^+$ 225.1761, found 225.1755.

4.7.34. N^1-(2-Chlorophenethyl)-N^3,N^3-dimethylpropane-1,3-diamine (**47**)

Obtained as white oil, 75% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.34 (dd, J = 7.6, 1.5 Hz, 1H), 7.24 (dd, J = 7.6, 1.5 Hz, 1H), 7.18 (td, J = 7.6, 1.5 Hz, 1H), 7.14 (td, J = 7.6, 1.5 Hz, 1H), 2.93 (t, J = 7.2 Hz, 2H), 2.87 (t, J = 7.2 Hz, 2H), 2.68 (t, J = 7.1 Hz, 2H), 2.29 (t, J = 7.1 Hz, 2H), 2.19 (s, 6H), 1.65 (p, J = 7.1 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) 137.9, 134.3, 130.9, 129.7, 127.7, 126.9, 58.2, 49.5, 48.3, 45.7 (×2), 34.3, 28.2. HRESIMS(+): m/z calculated $[C_{13}H_{22}Cl_1N_2]^+$ 241.1466, found 241.1465.

4.7.35. N^1-(3-Chlorophenethyl)-N^3,N^3-dimethylpropane-1,3-diamine (**48**)

Obtained as white oil, 75% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.28 (t, J = 7.7 Hz, 1H), 7.26 (s, 1H), 7.24 (d, J = 7.7 Hz, 1H), 7.16 (d, J = 7.7 Hz, 1H), 2.95 (t, J = 6.9 Hz, 2H), 2.88 (t, J = 6.9 Hz, 2H), 2.77 (t, J = 7.0 Hz, 2H), 2.35 (t, J = 7.0 Hz, 2H), 2.20 (s, 6H), 1.72 (p, J = 7.0 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) 141.9, 134.4, 129.9, 129.0, 127.2, 126.6, 58.4, 50.8, 48.8, 45.5 (×2), 35.6, 27.1. HRESIMS(+): m/z calculated $[C_{13}H_{22}Cl_1N_2]^+$ 241.1466, found 241.1461.

4.7.36. N^1-(4-Chlorophenethyl)-N^3,N^3-dimethylpropane-1,3-diamine (**49**)

Obtained as white oil, 75% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.24 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 2.83 (t, J = 7.1 Hz, 2H), 2.76 (t, J = 7.1 Hz, 2H), 2.63 (t, J = 7.2 Hz, 2H), 2.26 (t, J = 7.2 Hz, 2H), 1.62 (p, J = 7.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) 138.8, 132.0, 130.2 (×2), 128.6 (×2), 58.2, 51.1, 48.4, 45.6 (×2), 35.9, 28.1. HRESIMS(+): m/z calculated $[C_{13}H_{22}Cl_1N_2]^+$ 241.1466, found 241.1463.

4.7.37. N^1-(3-Chloro-4-methoxyphenethyl)-N^3,N^3-dimethylpropane-1,3-diamine (**50**)

Obtained as pale yellow oil, 68% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.22 (s, 1H), 7.07 (d, J = 8.3 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 3.88 (s, 3H), 2.85 (t, J = 7.0 Hz, 2H), 2.75 (t, J = 7.0 Hz, 2H), 2.69 (t, J = 7.1 Hz, 2H), 2.29 (t, J = 7.1 Hz, 2H), 2.17 (s, 6H), 1.66 (p, J = 7.1 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) 153.6, 133.1, 130.5, 128.1, 122.5, 112.4, 58.4, 56.4, 51.1, 48.7, 45.6 (×2), 35.0, 27.7. HRESIMS(+): m/z calculated $[C_{14}H_{24}N_2O_1Cl]^+$ 271.1571, found 271.1563.

4.7.38. N^1-(3,4-Dichlorophenethyl)-N^3,N^3-dimethylpropane-1,3-diamine (**51**)

Obtained as pale yellow oil, 70% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.34 (d, J = 8.2 Hz, 1H), 7.30 (d, J = 2.0 Hz, 1H), 7.03 (dd, J = 8.2, 2.0 Hz, 1H), 2.83 (t, J = 7.1 Hz, 2H), 2.74 (t, J = 7.1 Hz, 2H), 2.64 (t, J = 7.1 Hz, 2H), 2.27 (t, J = 7.2 Hz, 2H), 2.17 (s, 6H), 1.62 (p, J = 7.1 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) 140.7, 132.4, 130.8, 130.4, 130.2, 128.3, 58.2, 50.8, 48.4, 45.7 (×2), 35.7, 28.1. HRESIMS(+): m/z calculated $[C_{13}H_{21}Cl_2N_2]^+$ 275.1076, found 275.1073.

4.7.39. N^1-(2,4-Dichlorophenethyl)-N^3,N^3-dimethylpropane-1,3-diamine (**52**)

Obtained as white oil, 80% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.37 (d, J = 2.1 Hz, 1H), 7.25 (d, J = 8.2 Hz, 1H), 7.19 (dd, J = 8.2, 2.1 Hz, 1H), 2.97 (t, J = 7.5 Hz, 2H), 2.91 (d, J = 7.5 Hz, 2H), 2.76 (t, J = 6.8 Hz, 2H), 2.33 (t, J = 6.8 Hz, 2H), 2.17 (s, 6H), 1.70 (p, J = 6.8 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) 134.9 (×2), 133.0, 132.1, 129.5, 127.3, 58.5, 48.9, 48.8, 45.5 (×2), 33.2, 27.0. HRESIMS(+): m/z calculated $[C_{13}H_{21}Cl_2N_2]^+$ 275.1076, found 275.1079.

4.7.40. N^1-(2,6-Dichlorophenethyl)-N^3,N^3-dimethylpropane-1,3-diamine (**53**)

Obtained as white oil, 75% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.27 (d, J = 7.6 Hz, 2H), 7.06 (t, J = 7.6 Hz, 1H), 3.12 (m, 2H), 2.83 (m, 2H), 2.71 (t, J = 7.3 Hz, 2H), 2.31 (t, J = 7.3 Hz, 2H), 2.21 (s, 6H), 1.67 (p, J = 7.3 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) 136.3, 135.7, 128.3 (×2), 127.9 (×2), 58.2, 48.1, 47.9, 45.7 (×2), 32.2, 28.2. HRESIMS(+): m/z calculated $[C_{13}H_{21}Cl_2N_2]^+$ 275.1076, found 275.1077.

4.7.41. N^1-(2-Chloro-6-fluorophenethyl)-N^3,N^3-dimethylpropane-1,3-diamine (**54**)

Obtained as yellow oil, 70% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.15 (d, J = 8.1 Hz, 1H), 7.11 (td, J = 8.1, 5.9 Hz, 1H), 6.95 (td, J = 8.1,

1.3 Hz, 1H), 2.98 (t, $J = 7.5$ Hz, 2H), 2.84 (t, $J = 7.5$ Hz, 2H), 2.69 (t, $J = 7.1$ Hz, 2H), 2.30 (t, $J = 7.1$ Hz, 2H), 2.20 (s, 6H), 1.66 (p, $J = 7.1$ Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) 162.2, 135.3, 127.9, 126.2, 125.33, 114.1, 58.2, 48.6, 48.1, 45.7 (×2), 28.2, 27.4. HRESIMS(+): *m/z* calculated $[C_{13}H_{21}N_2Cl_1F_1]^+$ 259.1371, found 259.1375.

*4.7.42. N^1,N^1-Dimethyl-N^3-(3-(trifluoromethyl)phenethyl)propane-1,3-diamine (**55**)*

Obtained as yellow oil, 55% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.46 (m, 2H), 7.43–7.38 (m, 2H), 2.87 (m, 4H), 2.66 (t, $J = 7.1$ Hz, 2H), 2.27 (t, $J = 7.1$ Hz, 2H), 2.17 (s, 6H), 1.63 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) 143.2, 141.3, 132.3, 128.9 (×2), 125.5, 123.1, 58.2, 51.2, 48.4, 45.6 (×2), 36.4, 28.1. HRESIMS(+): *m/z* calculated $[C_{14}H_{22}N_2F_3]^+$ 275.1729, found 275.1731.

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Appendix A. Supplementary material

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2013.12.050.

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